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Shifting Collaborations and the Quest for Legitimacy: Observation of Regenerative Medicine Research in Japan

Koichi Mikami

Science, Technology and Innovation Studies,

University of Edinburgh

Introduction

On 12 June 2012, the Japanese Society for Regenerative Medicine (JSRM) held a public lecture in Yokohama, a harbour city about 30 kilometres south of Tokyo, as part of its 11th Annual Congress. The congress was one of the biggest events in the field of regenerative medicine research in several years, not just because it was a once-a-year opportunity for Japanese researchers in this growing field to gather and present their latest achievements but also because it was held consecutively with the annual meeting of the International Society for Stem Cell Research (ISSCR), the international academic society of stem cell scientists. Approximately 800 people attended this two-hour lecture (11th Congress of JSMR, 2012), and I was one of them. In the conference room where the lecture took place, I saw a large number of patients, some of whom were in wheelchairs, their families and caretakers, the recognisable faces of some researchers surrounded by the flocks of businesspeople and many individuals whom I did not recognise and whom possibly the category of 'public' applies to.

The programme of the lecture listed three academic speakers along with a non-academic commentator. Yoshiki Sawa, the chair of this event and also that of the JSRM annual congress, invited the first speaker Shinya Yamanaka, a stem cell scientist known for his reprogramming

technique to create induced pluripotent stem (iPS) cells.[1] Yamanaka opened his talk with casual conversation with the chair and the non-academic commentator Takuro Tatsumi – a Japanese actor later revealed to be a senior alumnus of the high school that Yamanaka himself attended – and then explained his future visions of iPS cell research. As soon as he finished his talk he had to leave the room, and the lecture moved on to the second speaker Teruo Okano, a biomedical engineer who developed a technique called 'cell sheet engineering'[2] and who is also the president of the JSRM. In his presentation, he demonstrated various achievements of his research group and presented his vision of making 'organ factory', which is a manufacturing approach to produce artificial tissues and organs for transplantation therapy. The final speaker was Sawa himself, who is a cardiovascular surgeon renowned for his experiences in heart transplantation. In his talk, three other individuals not listed on the programme approached the stage: they were Sawa's former patients who received 'myoblast cell sheet therapy'[3] for heart disease, invited as panel speakers to comment on their experiences and explain how the therapy improved the quality of their life.

Each of these speakers at this JSRM public lecture, including Sawa's former patients, is appropriate for the main theme of regenerative medicine research in Japan and, given that Yamanaka became the president of the ISSCR after its Yokohama meeting, the selection of the speakers indicated the chair's intention to present 'the state of art' in this research field to the curious public. Yet, this lecture simultaneously embodied 'the state of collaboration' in this field, as each academic speaker has a different disciplinary background, representing a different stance in regenerative medicine research, and, from a social scientist's perspective, the question of why they were all there to speak

[1] Yamanaka invented a technique to induce the similar biological properties to embryonic stem cells to already-differentiated cells of an adult body, creating iPS cells, and for this invention he received the Nobel Prize in 2012.

[2] Cell sheet engineering is an bio-engineering technique to culture cells in a special petri dish with temperature-responsive polymer coating, which allows researchers to collect cells in a form of a sheet, making it easy to use for both research and therapeutic purposes.

[3] Myoblast cell sheet therapy is a clinical application of the abovementioned cell sheet engineering, and myoblast cells obtained from the patient's thigh were cultured as a cell sheet, which was applied to the patient's heart to strengthen its function.

is worthy of a sociological investigation. Furthermore, the specific audience whom each of them tried to engage also seems reflective of the structure of this research field.

While collaboration in research can be studied at various levels (see Katz and Martin, 1997), in this chapter I examine collaborations in the field of regenerative medicine research in Japan as the configurations of 'clusters', or formal and informal social ties and groupings of different actors. The field of regenerative medicine research is not only interdisciplinary but also argued to lack an agreed-upon definition (Morrison, 2012), and by examining how the clusters have evolved in Japan since 2000, I aim to assess the symbolic significance of the 2012 JSRM lecture for this emerging field. The collaborations in the field are not necessarily directed towards the publication of a scientific article but more likely towards the invention of medical technology, and such collaborations are difficult to assess using bibliometric approaches, as no 'list' of collaborators would be produced in the attainment of this goal (Katz and Martin, 1997). Thus, in my analysis, I draw on the qualitative data collected during five years of sociological fieldwork, including in-depth interviews, reviews of scientific articles and policy documents, and observations at meetings and conferences, all conducted from late 2007 through early 2012.

Throughout the chapter, I employ the term 'cluster' to describe social ties and groupings observed in this field for several reasons. Firstly, despite the academic speakers' distinctive disciplinary backgrounds, the term 'cluster' is more fitting than 'discipline' because disciplines are the categories emerged as 'the result of specialization in scientific practice, in terms of the scientific questions pursued and the hypothesis addressed' (Penders et al., 2008: 748). The speakers under this study share practices and visions not only with their fellow scientists but also with many other actors, including funding bodies, corporate partners and even patients and their families. Moreover, the boundaries of clusters are neither self-evident nor fixed, and for this reason even those clustered themselves may not be conscious of their belonging to one or other. As indicated above, the clusters

in this field have evolved over the last decade or so, and as such different constituents now than several years ago without them necessarily changing their practices. It is also important to emphasise that while the boundaries of clusters are not evident at the first blush, they are certainly there, and reflecting this point I find the term 'cluster' more appropriate than 'network', which often refers to a linkage of different actors. To refer to what creates the sense of belonging to each cluster, I deploy the word 'style', following Fujimura and Chou's phrase of 'styles of practice', defined as 'historically located and collectively produced work processes, methods and rules for constructing data and theories and verifying theories' (1994: 1017; also cited in Penders et al., 2008). Yet again, I do not limit the use of this term to that of 'scientific' practices and instead apply it to a spectrum of practices and visions involved in regenerative medicine research.

The following sections are ordered nearly chronologically. This study starts in the year 2000, when regenerative medicine research became part of a large-scale, national project in this country. As a result of this turn-of-the-millennium policy initiative, Japanese regenerative medicine research came to resemble 'big science' observed in the latter half of the twentieth century, characterised not only by its volume of funding invested and its number of scientists committed but also by its alignment with non-scientific goals, be it political, economic, or military, and the effort to coordinate different sets of expertise to attain them (e.g. Kelves, 1995; Galison, 1992; Galison and Hevly, 1992). Thus, the year 2000 serves as a reasonable starting point for addressing complex interactions of various actors in this field. As previous studies on research collaboration suggest, becoming 'big science' is not always positive and may come with some costs (e.g. Katz and Martin, 1997; Vermeulen et al., 2010; Weinberg, 1961). Such costs are not only financial, related to the effort of coordinating the collaboration, but also social, associated with the tension arisen within it. While perhaps desirable for maintaining diversity in the field and granting some autonomy to scientists (Vermeulen et al., 2010), the conventional style of small laboratory-based life science research poses significant hurdles for regenerative medicine research in Japan to be coordinated as 'goal-sharing' big science.

Therefore, the actors under this study have actively (re-)configured their collaborations so as to achieve legitimacy in this field.

The quest for legitimacy has been a complex process not only because the research field is interdisciplinary but also because of the commitment of the government in the early 2000s rejecting the style of 'pure' science, in which one's scientific legitimacy is achieved by conducting good research and gaining credibility in the scientific community, and instead demanding the shift toward 'clinically relevant' research (cf., Albert and Kleinman, 2011; Bourdieu, 1999; Latour and Woolgar, 1979; Maienschein, 1993). Yet, the cluster of stem cell scientists had difficulties with adjusting their rules and hence changing their styles; biomedical engineers and surgeons, in contrast, came together as another cluster, appreciating the value of patient participation, though it was only possible under a specific legal condition. This situation changed dramatically in 2007 when Yamanaka created human iPS cells, and this event offered a new interpretation of 'clinical relevance'. Having been less successful in its commitment with stem cell science, the government was keen to seize this emerging opportunity and introduced new rules in this field, which again provoked unexpected responses from different research clusters. This Japanese case therefore presents the struggle of shaping a scientific field with the commitment of non-scientific actors, the government in particular. If 'big science' is to be understood as the coordination of research for non-scientific goals (Galison, 1992), then life science research will likely have more of it; yet, as this case shows, there can be a counter move to retain its smallness and hence its purity.

From Stem Cell Science to Regenerative Medicine Research

The new millennium was an important turning point for Japanese science and technology policy. The nation experienced the burst of economic bubble in early 1990s, and little recovery in its economy was observed in its ensuing years (cf., Hayashi and Prescott, 2002). Japan has few natural resources to capitalise on, and hence the government viewed advances in science and technology as

promising sources for the nation's recovery, just as they were for the nation's dramatic economic growth in 1970s and 1980s. To promote science and technology within the country, the government enacted the Science and Technology Basic Law and then established the Council of Science and Technology Policy as its internal advisory body in 1995. The Law (1995) stipulates that, upon its consultation with the Council, the government must publish Science and Technology Basic Plans (STBPs) every five years, explicating national strategies for promoting science and technology and also for coordinating plans of related ministries. The first STBP was published in 1996, but this document simply pointed out the need for building national research capacities, suggesting that the size of research population needed to increase and that better research infrastructure ought to be developed (STBP, 1996). It required several more years before the government strategically committed to promoting certain areas of science, and both the Millennium Projects launched in 2000 and the second STBP published in 2001 marked this policy shift.

The Millennium Projects were large-scale government research initiatives focusing on three key themes in modern society – information, ageing and environment. By addressing these themes, research projects were expected to 'resolve the problems that human race would face' and 'result in technological innovation developing new industries' (Kantei, 1999). The government called for research proposals in 1999, and the selected projects commenced in April 2000. As part of the Millennium Genome Project, stem cell science was conducted over five years, corresponding to the theme of ageing. A significant milestone in this national project was the establishment of RIKEN Center for Developmental Biology (CDB) in the harbour city of Kobe in 2000, which has been a key figure in Japanese regenerative medicine research since then. The second STBP (2001) endorsed the visions underlining the Millennium Projects and listed information technology, environmental sciences and life sciences as the national priorities along with five other items. In the section of life sciences, the government clearly stated that it would focus on 'cellular biology, so as to achieve advances in organ transplantation and regenerative medicine' (STBP, 2001: 22–3). Thus, this

document officially listed regenerative medicine as an important target for Japan's science and technology.

Enjoying substantial political support for the Millennium Genome Project, Japanese stem cell science made significant progress over the five years of period but its progress was not fully aligned with the original intent of the government. As suggested in the second STBP, the government expected stem cell science to produce 'clinically useful' knowledge, but many research achievements were in animal-based studies on cellular development, differentiation and regeneration. The interim assessment report of the Millennium Genome Project published in 2003 highlighted the need for clear plans to make a transition from basic science to applied research (Kantei, 2003). Like other areas of basic biology, animal cells have been widely used to study biological mechanisms of cellular development, differentiation and regeneration, but, in contrast, human cells, which are critical to understand clinical implications of such mechanisms, were difficult to obtain and only a handful of researchers at university hospitals had access to the cells of donor patients. Despite the significance of RIKEN CDB's location adjunct to a research-focused hospital, stem cell scientists had difficulties with collaborating with medical doctors, who tend to be more interested in improving therapeutic approaches (cf., Cambrosio et al., 2006). The final assessment report published in 2006 stated that the outcomes of stem cell science were 'not ready for clinical applications', leading to the conclusion that the next step was to consider the move into 'translational research' (Kantei, 2006).

Stem cell scientists were not entirely responsible for this mismatch, and the case of human embryonic stem (hES) cell research demonstrates how policy decisions also contributed to it. The growing expectation for stem cell science to make medical innovation at the beginning of the new millennium was partly the result of the establishment of the first hES cell lines by the American scientist James Thomson in 1998. This special type of stem cells has two significant abilities, an ability to be any kind of cells constituting human body and the other to proliferate unlimitedly.

These abilities would potentially offer significant advantages for their therapeutic use. However, how nations reacted to these stem cells varied considerably due to the ethical concerns about their research use (Gottweis et al., 2009). The US government announced in 2001 that the National Institutes of Health would only support hES cell research using already established cell lines, and in contrast the UK government authorised research on hES cells for the purpose of developing new treatments under its Human Fertilisation and Embryology (Research Purposes) Regulation 2001. In the same year, the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) also manifested its attitude toward these cells in its Guidelines for Derivation and Utilization of Human Embryonic Stem Cells.

The Guidelines (2001) did not ban hES cell research but rather made it difficult to undertake it in Japan particularly for two reasons. Firstly, the Guidelines stated that 'a human embryo is a beginning of life' and that 'human ES cells have the potential to differentiate into any types of human cells' (2001: Article 3). Following this idea, the Guidelines required both derivation and use of hES cells to pass a dual review process: firstly by the institutional review board of one's organisation and then by the Ministry, thereby rendering hES cell research both labour-intensive and time-consuming. Secondly, the Guidelines undermined the 'therapeutic promise' of hES cells – limiting the need for hES cell research in Japan and rejecting the powerful argument for making hES cell available for research in some other countries (cf., Rubin, 2008). By stating that 'clinical research applying human ES cells or cells originated from them to the human body, and utilization of them in medicine and in its related fields' ought not to be carried out 'until specific criteria other than the Guidelines have been established' (2001: Article 2.2), they caused great uncertainty over medical significance of these cells. This policy decision discouraged the researchers to conduct hES cell research. As a result, Japanese stem cell science progressed without much action in hES cell research (Nakatsuji, 2007), and many researchers chose to study mouse ES cells for their basic research, which exhibit fewer ethical concerns and have been available for long time. Thus, the Guidelines enlarged the gap between basic and applied research in stem cell science.

In accordance with the original STBP policy vision of promoting the production of clinically useful knowledge, MEXT decided to push other areas of stem cell science towards a more clinical orientation, rather than overturning its decision on hES cell research, and launched the 'Project for Realization of Regenerative Medicine' in 2003. As its title shows, this project was designed to focus on clinical applications of stem cells, and the two of its three principal investigators were based at university hospitals, encouraging the kind of collaboration that the Millennium Genome Project was not successful to initiate. Yet, the project leader and the third principal figure were nominated from RIKEN CDB and hence the project was complementary to stem cell science in the Millennium Genome Project, which ended in 2005. Among various non-hES cells, mesenchymal and haematopoietic stem cells in particular were considered to be promising sources for regenerative medicine in this project, and this led to the establishment of a cord blood stem cell bank. This bank was expected to provide stem cell scientists with easy access to ethically-sourced human multipotent stem cells, just as the UK Stem Cell Bank was designed for hES cells (Stephens et al., 2008). This project ran its first term for five years, and it was in its fifth and final year when Yanamaka's research group announced its creation of human iPS cells – an innovation that dramatically changed the state of Japanese regenerative medicine research.

Collaborations at University Hospitals

While MEXT struggled to let stem cell scientists work on human cells, several other actors were actively working on them already, and the works of Teruo Okano and Yoshiki Sawa illuminates this side of the field. Okano developed the abovementioned 'cell sheet engineering' technique in the mid-1990s. When cells are cultured in a petri dish, usually an enzyme needs to be applied to isolate them for collection but its application also causes some damage to the cells. To resolve this problem, Okano invented a special petri dish with temperature-responsive polymer coating: this invention allows the cultured cells to be collected in the form of a sheet simply by changing its temperature

without causing any damage (Okano et al., 1995). The cell sheet removed from the petri dish can also be applied directly onto the site of the body in need of therapy, rather than releasing the cells into the body by injection. This new approach is expected to be more effective for therapy because most cells stay at the intended site and perform their functions, while the injection approach must depend on body's biological mechanisms to guide the cells to the deformed site.

Okano not only developed this technique but also promoted its clinical applications actively. In 2001, he established a spin-off company to make his petri dish available for research use. Based at a medial university, his research group also teamed up with surgeons and initiated clinical research using the technique. Once he began such research, some medical doctors from other university hospitals became interested in collaborating with his group. The early successes of such collaborations were on cornea and heart therapies. Severe corneal diseases can be treated by transplantation and this is a well-established medical practice, but the scarcity of corneal tissues for transplantation has been a major challenge. Okano's technique allows a doctor to culture the cells obtained from a patient's mouth in the form of a sheet, which can be transplanted back to the patient's cornea, rather than depending on cornea donation. Similarly, cells procured from a patient's thigh can be used to produce cell sheets, which are then applied to the heart to treat heart failure. This is an attractive alternative to heart transplantation in Japan, where cadaver donors are scarce for its socio-historical reasons (cf., Lock, 2002). Yoshiki Sawa was one of Okano's main collaborators for this myoblast cell sheet therapy, and in fact the patients spoke in the 2012 JSRM public lecture were the first recipients of this therapy as part of the clinical research jointly conducted by Okano and Sawa.

These clinical studies of cell sheet therapies represent a different research cluster of regenerative medicine in Japan from that of stem cell science. They focused on adult somatic cells, which are already differentiated into certain lineages of cellular development, and mainly dealt with their structural matrices, rather than the mechanisms of cell expansion and differentiation. The style of

their practice was goal-oriented, which is stereotypic of engineering and medical sciences. This is not to suggest that all collaborators in this cluster shared a single goal. Instead, each of these actors had a personal goal and in order to attain it, collaboration was critical: while Okano, the biomedical engineer, had the special petri dish, he needed access to both the patients and their cells to prove the value of his invention as a tool for regenerative medicine. In contrast, Sawa, the surgeon, needed the petri dish and the skills in culturing cells to treat his seriously-ill patients, as donated organs were unlikely to be available for transplantation. Moreover, because this yet-to-be-approved therapy must be conducted as clinical research, the patients needed the surgeon and his authority in medicine to take part in it.

In this collaboration, each of the actors also had something to offer to the others. The biomedical engineer offered his petri dish, the patients their cells. While these two items are material components of this regenerative medicine approach, the space within a hospital, which only the surgeon could provide, was indispensable for making their collaboration. Until 2006, no guidelines on clinical research using human cells, other than international ethical guidelines, existed and just like any other medical practices the research was regulated under the Medical Practitioners Law, which is the legal basis of the medical licensing system in Japan. Under this law, the doctors reserve the discretionary right to decide how their patients ought to be treated, and are allowed to use drugs and devices not yet approved by the government. The condition for conducting clinical studies of regenerative medicine was only that both the patient and their cells had to remain under a doctor's control throughout the procedure. For this reason, the cells had to be cultured at a hospital. In other words, the collaboration for cell sheet therapy could not have taken place if the surgeon had been unable to offer the space for culturing the cells.

Hospital-based collaborations like this produced some clinically promising results but advances in clinical applications of adult stem cells have seldom led to commercial applications. As Okano's spin-off company represents, commercial actors existed already in the early 2000s and many of

them contributed to such collaborations in one way or another. However, for them, initiating the similar research procedure would have been a different issue. In clinical trials, for instance, companies must follow the Pharmaceutical Affairs Law, regulating manufacturing of drugs and devices, as well as the instructions of the Ministry of Health and Welfare (MHW)[4] on cellular products. The instructions (MHW, 1999) stipulate that a company must demonstrate both safety and efficacy of its product to start the phase-I clinical trial. However, as some company-based researchers complain, this requirement is not easy to meet. Firstly, efficacy may not be evident, even for the company, as pre-clinical studies only demonstrate the results from animal models and their relevance to human subjects is uncertain. Secondly, without clear criteria for product safety, the company is expected to be accountable for its product beyond its production line. Unlike in clinical research, a product must be delivered to a hospital, and the company has to demonstrate that its cellular product remains stable and safe even for this extra period of time. Furthermore, the company has to conduct the entire procedure in a strictly controlled working environment, which was not a condition necessary for clinical research at hospitals.[5] Therefore, despite their participation in the research cluster, many companies were not able to take advantage of it.

The Birth of Induced Pluripotent Stem Cells

Until 2006, the two clusters co-existed with little interactions in Japanese regenerative medicine research. One was the cluster of stem cell scientists, emphasising the biological mechanisms of cellular development, differentiation and regeneration, progressed with the government support since the beginning of the new millennium; and the other was that of biomedical engineers and medical doctors, who focused on the therapeutic use of adult somatic cells, with some success on

[4] The MHW was re-structured as the Ministry of Health, Labour and Welfare (MHLW) in the 2001 Central Government Reform.

[5] This policy gap between academic clinical research and industrial clinical trials existed until 2006, when the MHLW introduced its Guidelines on Clinical Research using Human Stem Cells, setting the similar standards for clinical research in hospitals (Guidelines, 2006; and also Matsuyama, 2008).

treating patients but not on delivering products to the market. However, neither of these clusters was able to present its legitimacy in this emerging field and to represent regenerative medicine research: the former cluster failed to produce clinically useful knowledge that the government demanded, and the latter only operated in a small scale under the privileged status of licensed doctors. The distance between the two clusters appeared as though the conventional division of 'basic' and 'applied' research was at work and was large as ever. However, the situation started to change in late 2006 when Shinya Yamanaka's research group invented a novel technique to reprogram the biological characters of adult cells and created what they called iPS cells from mouse skin cells.

Yamanaka and his colleague Kazutoshi Takahashi (2006) argued that their technique had the potential to resolve ethical issues of hES cell research because their cells exhibited the identical biological properties as ES cells, but there was a question about its applicability to human cells at that time. If only applicable to non-human animals, this technique would not differ much from previous cloning techniques and would fail to confirm its clinical relevance – from the government's perspective, this could have been merely another achievement in pure science. In 2007, however, Yamanaka succeeded in applying this technique to human skin cells and successfully demonstrated its potential clinical relevance (Takahashi et al., 2007). Within a couple of days of this announcement, MEXT sent its officers to Yamanaka to evaluate the implications of the technique and discuss how the Ministry could support his research further (Hishiyama, 2010). As Thomson's group in the US also reported its success in creating human iPS cells almost at the same time (Yu et al., 2007), MEXT sensed the intensity of international competition in this field and took responsibility for supporting his research, simultaneously allowing itself to claim credit for its future advancement.

Within the couple of months since Yamanaka's announcement, the government held several meetings and he was invited to explain how useful iPS cells would be for regenerative medicine and drug development. In these meetings, he suggested that forming a collaborative research network

would be indispensable if Japan were to compete against research universities in the US and elsewhere (Hishiyama, 2010). MEXT adopted this vision and established the 'All-Japan' research network for iPS cell research. Central to this network were the Center for iPS Cell Research and Application (CiRA), a research institute founded at Kyoto University for and directed by Yamanaka, and MEXT's Project for Realization of Regenerative Medicine. The Project started its second term in April 2008, and Yamanaka joined the three principal figures by becoming its fourth core researcher. With these developments, the focus of this project also shifted from multipotent stem cells to iPS cells, and Shinichi Kousaka, a senior medical scientist was appointed the new project leader. Yamanaka also became the director of two other research programmes focusing on iPS cells, one with the support of MEXT and the other with that of the Cabinet Office. Here, the collaborative network of iPS cell research was established under the government's initiative. While the members belong to different universities and research centres, they were expected to share their latest findings and research resources within this network and maintain Japan's leading position in this emerging field.

In addition to the political support, Yamanaka also enjoyed great public support. The news about his creation of human iPS cells circulated widely in the Japanese mass media – that a young Japanese scientist invented a new technique, resolving one of the significant challenges in cutting-edge life science, immediately brought massive popularity (cf., Shineha et al., 2010). Compliments from well-recognised political and religious leaders, like the US President and the Pope, also helped this phenomenon. The concept that iPS cells could allow one's cells to be utilised for treating one's own disease, thereby alleviating the problem of organ shortage, was another reason for its popularity in this country. To maintain and potentially increase this public support, MEXT has frequently held public events around its programmes of regenerative medicine research since the end of 2007, and all have been very well attended. The scene of audiences taking photos of Yamanaka has been common in such events, indicating Yamanaka's 'heroic' status, representing not only Japanese regenerative medicine research but also the community of science. His popularity among the public

served to re-vitalise the cluster of stem cell scientists and MEXT promised them another five years of its support, despite their persistent struggle to produce clinically useful knowledge.

During this remarkable period for the cluster of stem cell scientists, hospital-based collaborations also made some progress. Only several weeks after Yamanaka's announcement of creating human iPS cells, Sawa announced that his first myoblast-therapy patient had made a fast recovery and was de-hospitalised. Almost simultaneously, a start-up company Japan Tissue Engineering Co. Ltd. (J-TEC) completed the series of clinical trials and obtained manufacturing authorisation for its cellular-based product for the first time in Japan. Among commercial actors, this latter event was considered particularly as an important milestone for regenerative medicine in this country, as it demonstrated that culturing cells for therapeutic use was no longer confined to a laboratory space within hospitals. The scale of the political support as well as the growing public support to iPS cell research, however, did not prove advantageous to this cluster. Despite the progress made both at a hospital and in the industry, the impact of Yamanaka's success was so significant that the term 'iPS cell research' became used synonymously with regenerative medicine research in this country. This by no means suggests that Okano's research group did not receive any government support for its research – Okano also obtained a large grant for his cell sheet engineering to realise his vision of an 'organ factory' (CAO, 2009) – yet, neither Sawa nor Okano enjoyed the public support comparable to that of Yamanaka and iPS cell research.

In 2009, MEXT, being responsible for advancing iPS cell research and accountable for a substantial portion of its financial spending, published a roadmap illustrating the future trajectory of iPS cell research over then ensuing 10 years (2009). This trajectory reflected the visions that Yamanaka explicated originally in 2007 (cf., Hishiyama, 2010), and this document was produced after consultations with the key figures in the All-Japan research network for iPS cell research. It listed four research streams: two are mainly concerned about the quality of iPS cells, with the goals of improving the reprogramming technique and producing standardised cell lines; the other two focus

largely on applications, with the visions of the cells to be utilised in drug discovery and as regenerative medicine. However, it was soon revealed that the timelines suggested in this roadmap were almost impossible to meet – even from the viewpoints of the members of the research network. While stem cell scientists appeared to have achieved their legitimacy in this field owing to both political and public support, there was a growing concern among them that another failure to meet the expectation can easily overturn this situation.

A major reason for this perceived impossibility was that collaboration necessary for attaining the goals set out in the roadmap proved difficult to implement. To promote the use of iPS cells for drug discovery, for example, the cells obtained from patients must be stocked at a cell bank and made available within the network. However, many researchers were reluctant to deposit their iPS cells until they publish several articles on them. Despite MEXT's political attempt to set common goals for the iPS cell research network and to turn its projects into 'big science' working toward them, the researchers had little incentive, if any, to share their valuable resources because their personal as well as project's merit was evaluated on the basis of peer-reviewed publications and possibly on the number of patents. Principal investigators, moreover, could not afford to let publication opportunities slip away, as they were responsible for the careers of their junior laboratory members. While this resource sharing problem did not totally abandon the cross-laboratory collaborations in the field, the researchers had to be careful choosing with whom they collaborate, necessarily involving a formal mode of contract, such as material transfer agreement, just as the conventional 'small' life science research. Therefore, the laboratory-oriented style of stem cell science posed a major hurdle for developing 'big-science' collaboration that Yamanaka and MEXT envisioned in establishing their All-Japan network of iPS cell researchers.

Bridging the Gap by Building a Highway

Having publicised its expected trajectory in iPS cell research in 2009, MEXT became desperate to meet its targets. Some progress were made in the studies for improving the reprogramming technique and also for standardising iPS cells, as they were projects that Yamanaka and his new research centre CiRA played the central roles. Yamanaka's public popularity, coupled with his medical background, also gave him access to some rare disease patients and allowed his group to advance drug discovery research using the cells obtained from them, though the scale of this work seem smaller than originally planned.[6] A significant delay was observed particularly in the research stream for applications of iPS cells as regenerative medicine, and only a few areas, such as retinal regeneration, are expected to start their clinical research in the coming years. To reduce this delay, MEXT and the Ministry of Health, Labour and Welfare (MHLW) launched a new programme called the Regenerative Medicine Highway in 2011.

This Highway programme was originally proposed by MEXT (2010) to overcome what it called the 'Death Valley' in regenerative medicine, which prevents the transition from basic to applied research. In this programme, the two ministries harmonise their financial and other support for selected research projects and allow them to make seamless transitions from pre-clinical to clinical studies – a change needed to hasten the development of regenerative medicine. MEXT called for proposals in four distinctive categories: short-term projects aiming to start clinical research within three years; mid- or long-term projects targeting clinical research in five to seven years; projects set to provide technical support for research initiatives, including the Project for Realization of Regenerative Medicine; and projects studying and resolving the ethical challenges in regenerative medicine. Thus, the Highway programme is designed not only to provide policy support to independent research projects but also to establish common resources for their smooth running, and in the first selection procedure, a total of 10 projects were chosen for its funding.

[6] Kyoto University established the Division for iPS Cell Application Development within its hospital in 2011 to be the contact point for patients willing to donate cells for iPS cell research.

Among these 10 projects, four were short-term and four were mid- and long-term. Overall, four of the 10 focus on clinical applications of iPS cells; yet retinal regeneration was the only such study selected for the short-term,[7] reflecting delayed progress in iPS cell research. The three other short-term projects aim to develop clinical applications of adult stem and somatic cells, instead of iPS cells, and all have a medical researcher at a university hospital as their principal investigator, indicating the two ministries' intention to integrate the two clusters. Furthermore, a project aiming to develop clinical applications of hES cells was also selected for the mid- and long-term projects, alongside the three others focusing on iPS cells.[8] As it was once commonly suggested that iPS cells would eliminate the need for hES cells, the inclusion of this research project within the Highway programme indicates a dramatic shift in the field of regenerative medicine research in Japan: investigators and funders alike are becoming more open to different styles of practices, so long as they are considered to be promising avenues for its advancement with some clinical relevance.

Neither Okano nor Yamanaka is part of this Highway programme. Yet, a few projects aim to combine cell sheet engineering and iPS cells, and the medical researchers leading such projects, including Sawa, may bridge the gap that for a decade existed between the two clusters in this country. This application-oriented programme also allows commercial actors to participate, though they still perform supportive roles in the projects. While it is a collection of independent research projects, the collaboration between MEXT and the MHLW in the policy domain has provided some common grounds for regenerative medicine research and seemed to have created an accommodating environment for different styles of practices.

[7] This research project is led by Masayo Takahashi at RIKEN CDB and the clinical studies are to be conducted at the neighbouring hospital, justifying its establishment about a decade ago in the Millennium Project and its visibility in regenerative medicine research since then.

[8] MEXT (2009) revised the Guidelines for Derivation and Utilization of Human Embryonic Stem Cells in 2009 and clinical applications of pluripotent stem cells, including both hES cells and iPS cells, became permitted, but the main reason behind this decision was to allow those of iPS cells.

This shift, however, does not seem to bring about the convergence of the two clusters. In a MEXT committee meeting on stem cell science and regenerative medicine research in early 2012, a committee member commented that too much attention has been paid to iPS cells – particularly to their clinical applications – and that the abovementioned Highway programme to some extent relieved the burden on stem cell scientists, allowing them to retain their original interest in the biological mechanisms of stem cells. This comment indicates that the bridge between the two clusters is leading to their re-configuration, instead of their convergence: only the part of iPS cell research that is more compatible with the goal-oriented style of the other cluster is segregated from the mainstream stem cell science and can be merged with the cluster developed in university hospitals. Hence, this re-configuration would not only allow stem cell scientists to maintain their original style of pure science but also legitimise it by dissociating them from the policy emphasis on producing clinically useful knowledge.

Again, this was not what Yamanaka envisioned when he proposed the All-Japan iPS cell research network back in late 2007, and his dissatisfaction with the state of collaboration in regenerative medicine research in Japan prompted him to recruit established researchers from other research groups within the network and enlarged his community at CiRA. To overcome the challenges that laboratory-based stem cell science posed for turning Japanese regenerative medicine research into 'big science', he attempts to expand his research group and cover most aspects of iPS cell research at his centre. Establishing himself as a leader of iPS cell research may be an effective approach to facilitate research coordination in this field and direct it toward the goals that he envisioned and MEXT publicised, but, as suggested at the beginning of this chapter, there can be cost in 'big science' – at least, he becomes responsible for the careers of a large number of researchers, many of whom have to obtain a new post before the government funding ends. Whether he will succeed in both coordinating research activities and attaining the original goals remains uncertain.

Discussion and Conclusion

In her study of research collaboration, Maienschein describes that 'researchers collaborate for a variety of intellectual and social reasons: to get help, to combine expertise, to gain credibility, or to create a community' (1993: 182). While each of these reasons may be applicable in any instance of research collaboration, the consistent rationale for collaborations in regenerative medicine research in Japan seems to have been the quest for legitimacy. To understand this, it is important to distinguish 'legitimacy' from 'credibility'. In their ethnographic study, Latour and Woolgar (1979) argue that the circle of credit is central to research and that scientists invest their credit, obtained from various activities in research, in earning themselves the right to do more research – for instance, by obtaining research grants, buying the latest equipment and publishing journal articles. In collaboration, Maienschein (1993) also suggests, credibility may also be shared and expanded. Thus, 'credibility' in science works like one's property, which can be obtained, possessed, invested and even shared. From this point of view, the idea of credibility resembles Bourdieu's (1999) idea of 'scientific capital', which functions just like other kinds of social capital, while specific to the 'field' of science: one accumulates by living as part of the community – receiving trainings, conducting research and presenting its result allow one to be recognised as part of the community from the peers. In contrast, 'legitimacy', for Bourdieu (1999), is about the power within the community, which must be achieved by accumulating scientific capital and possibly other social ones relevant to a field of science and ought to be exercised by influencing the peers. Achieving legitimacy is important because it is about the power not only to set the rules of its community but also to define the field.

One's scientific capitals can only be valuable so long as the community follows the same rule and recognise their value (see also Albert and Kleinman, 2011). In an interdisciplinary field, like regenerative medicine research, however, the rules are not clear – researchers may adopt different rules (cf., Panofsky, 2011). Furthermore, in this Japanese context, the value of scientific capitals seemed depreciated when stem cell science became part of the Millennium Genome Projects in

2000. The strong commitment of the government and its emphasis on ‘clinically useful’ knowledge forced stem cell scientists to adopt new rules of the game. However, with the structure of its community remained the same, they simply followed the original rules of ‘pure’ science, in which scientific credibility counts the most, and pursued their research on biological mechanisms of cellular development, differentiation and regeneration, mostly based on animal models. A few years later, they were criticised for not being ‘clinically relevant’. Despite their credibility accumulated during the Millennium policy initiative, they therefore failed to achieve legitimacy and set their own rules of the game. MEXT then launched the Project for Realization of Regenerative Medicine in 2003 urging them to re-structure the community, again insisting the importance of clinical usefulness. Yet again, they struggled to team up with medical doctors, who do not value their scientific capitals much, resulting in upholding of their own cluster.

In contrast to such struggle of stem cell scientists, biomedical engineers experienced little difficulties working with active surgeons. They had been developing novel techniques on less complex adult somatic cells, and some of the techniques were quite ready for clinical studies. Surgeons, interested in treating patients primarily, were willing to collaborate with them and to test such techniques. This hospital-based collaboration was only possible where patients agree to participate in the studies, and hence patient participation served as the valuable social capital for them, indicating relevance of their research as regenerative medicine. However, they were not successful enough (or maybe they were not fast enough) to achieve legitimacy and set the rules in the field: their collaborations remained confined to hospitals spaces, where the discretionary right of medical doctors is reserved.

This situation changed dramatically in 2007 when Yamanaka announced the creation of human iPS cells. The development of the reprogramming technique in 2006 allowed him to accumulate credibility within the community of stem cell science, and then by demonstrating its applicability to human cells he successfully translated this credibility into social capital relevant to the field of

regenerative medicine research. Unlike hospital-based collaborations, he has not been able to acquire much social capital of patient participation through iPS cell research, but instead by publicising his visions of using the new cells for drug discovery and as regenerative medicine he managed to frame the general public as a group of potential patients, who would benefit from advances in iPS cell research, and turn their support as the evidence of its clinical relevance. As discussed in the sociology of expectations (e.g. Brown et al., 2000; Brown and Michael, 2003), he mobilised resources in the present by presenting a scenario of the future – the enthusiastic support from healthy members of the public might not have been recognised as the valuable 'capital', unless they recognised usefulness of his research and accepted that it was clinical rather than basic (cf., Shineha et al., 2010).

MEXT attempted to affirm Yamanaka's legitimacy and make his visions as the basis of the new rules in this field by establishing the All-Japan network for iPS cell research. Yet, its attempt failed: the tension arisen within the network left the visions 'unrealistic' and hence its future value left unverified. The Ministry reacted to this by launching another programme with the MHLW. Their goal-oriented Highway programme, as discussed in the studies of innovation policy (e.g. Gibbons et al., 1994), enrolled diverse actors, including not only the members of the stem cell science cluster but also those of the other cluster, who have accumulated capitals of patient participation over the years. To some extent, MEXT managed to bridge the gap between the two clusters. Yet, some stem cell scientists considered this programme as a long-awaited opportunity to re-establish their own field where credibility is intertwined closely with legitimacy, that is, the ideal world of 'pure' science (cf., Bourdieu, 1999). Yamanaka, rather than participating in this programme and becoming part of the re-configured cluster, upholds his original visions of iPS cell research and tries to protect his legitimacy by expanding his own research centre.

According to Gieryn (1983), scientists often demonstrate their legitimacy by drawing the boundary against 'non-science' and by presenting themselves as the producers of 'valuable' knowledge. In

other words, they maintain the value of credibility in science by purifying the community (Bourdieu, 1999). However, as this study of regenerative medicine research in Japan shows, the value of life science research is increasingly tied to its 'clinical relevance', and patient participation is becoming a major resource for one's legitimacy. The boundaries of the clusters in this field therefore have been drawn and re-drawn to integrate the figures of patients as its main capitals. The integration of patient figures and hence the demonstration of clinical relevance, however, are more compatible with some styles of practice than others. Thus, biomedical engineers and surgeons have been able to maintain their style at the same time as they accumulate their capitals, while stem cell scientists insisting on their own style struggled to achieve legitimacy. Despite their dramatic revival since late 2007, some stem cell scientists have been keen to re-draw a boundary again between 'basic' and 'applied' research so as to go back to where they started in 2000.

This study also demonstrates that a field of science is being shaped not only by the researchers' attempt to draw its boundaries but also by the government's attempts to justify their policy decisions. This government's influence to some extent confirms mutual reliance between science and policy (e.g. Jasanoff, 1990; Shackley and Wynne, 1995), but it seems important for the government to commit the right kind of a cluster, or otherwise it needs to make the one it already committed right because researchers tend to form different clusters. This rightness again has to be defined by the rules of the game in the field. The Japanese government's commitment with stem cell science in early 2000s could have proved successful if this field was simply of 'pure' science: the researchers made significant advancement and obtained scientific credibility since the beginning of the new millennium. However, the emphasised importance of 'clinical relevance' posed it a significant challenge. Yamanaka's creation of human iPS cells provided the government an opportunity to re-configure the cluster and justify its commitment after its unsuccessful attempts of the Millennium Genome Projects and the Project for Realization of Regenerative Medicine.

However, the initiatives on iPS cell research also turned out to be not as successful as expected because of the persistent tension within the established research network. In his study of molecular biologists, Hackett (2005) argues that such tension is critical part of 'cooperative competition' in life science. Each research group in the network wanted to make breakthroughs and obtain credibility in the field, but staying in the cluster was a strategic decision for it to have access to newly created iPS cells and enjoy the substantial research support. Before it discloses its findings and shares the data and materials produced in its research, however, the group needs to make sure that it takes full advantage of them and is better positioned in setting the rules in the field than its cooperating competitors. While Chompalov and his colleagues argue that those 'who produces an innovative [style of practice] could well be making the collaboration's task more difficult' (2002: 760), therefore, researchers in an emerging field like this have strong motivation to develop an innovative style and set the rules for the field. This kind of tension might have been resolved, just like the healthy tension within a single laboratory, if the network had a clear 'leader' to take control over activities of its members.

This policy failure provided the background for Yamanaka's gradual shift away from the 'participatory' national network to the formal hierarchy at his research centre CiRA. As a director of the centre, Yamanaka is able to set rules and coordinate the work of its members toward the shared goals, reflecting his own visions. This can also be seen as a case of 'mezzo' science emerged from the bigger one (cf., Vermeulen et al., 2010). This kind of intra-organisational collaboration can be advantageous in several ways: its formal structure can introduce the division of labour among the researchers, which 'ensures a more effective use of their talents' (Katz and Martin, 1997: 14); their physical proximity can also allow them to share their skills and tacit knowledge, which may not be conveyed through published journal articles (Katz and Martin, 1997), and finally sharing of limited time and space of research facilities, just as the case of an accelerator laboratories (Champalov et al., 2002), would prompt them to have more communications. As a director of the centre, Yamanaka is also able to adopt a different set of criteria for assessing the contribution of each member from that

agreed within the cluster of regenerative medicine research. Just as MEXT and the MHLW designed in their programme, building technical and ethical resources available for its member researchers is considered to be critical for advancing this field further and Yamanaka seems keen to develop such non-scientific expertise within his research centre too.

Coordinating research activities of researchers can be a daunting task, but as Hackett (2005) suggest, a leader does not have to be good at everything but only needs to be good at articulation work, allowing its members to be part of the project with confidence in their future. The coming years will be a testament to coordination skills of Yamanaka, who have already shown his scientific excellence.

Thus, the 2012 JSRM public lecture was not only a showcase of the state-of-the-art research in this field but also that of the research clusters of which it consisted. Yamanaka engaged Takuro Tatsumi representing healthy members of the public, explained the values of his iPS cell research to the audiences and left the room. Having achieved the heroic status among the public, he had other businesses to do to maintain his legitimacy and to keep his research going. Left in the room were the two other academic speakers, Okano and Sawa. The biomedical engineer talked about his research accomplishments, which might be of interest to both academic researchers and commercial actors sitting in the room, who could be his future collaborators; their technical complication, however, discouraged most public audience to engage with his research directly. In contrast, the surgeon managed not only to demonstrate his past engagement with actual patients but also to build the link between the biomedical engineer and the public audience, serving as a 'host' for both. All the speakers tried to demonstrate their legitimacy in this underdetermined field of regenerative medicine research, but they did so in different ways reflecting their views on what is (and ought to be) valued in the field. Needless to say, no other stem cell scientist than Yamanaka spoke in this lecture, as he would have insisted that legitimacy could only be achieved by convincing fellow scientists and earning credibility from them, rather than engaging with the public audience.

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